23. (Withdrawn) A method of downmodulating the immune response comprising contacting a cell with an antibody-toxic moiety conjugate, wherein the antibody specifically recognizes CTLA4.

24. (Previously presented) The antibody-toxic moiety conjugate of claim 2, wherein the toxic moiety is a chemotherapeutic agent.

## REMARKS

The disclosure stands objected to because blanks are present in the specification on pages 4, 5, and 28 for ATCC and hybridoma designations of the CTLA4 antibodies. Applicants respectfully request that the objection be held in abeyance until such time as there is allowable subject matter.

### Status of the Claims

Claims 2-11 and 13-24 are pending. Claims 16-23 have been withdrawn from further consideration by the Examiner as being drawn to a non-elected invention. Claims 2-11, 13-15 and 24 are currently under consideration. Claim 2 has been amended herein to more particularly point out the invention. Support for this amendment is found on page 3, lines 6-10; page 12, line 8; page 67, lines 10-14; and page 86, lines 6-10. Claims 4 and 7 have also been amended herein to more particularly point out the invention. Support for the amendment to claim 4 can be found on page 10, lines 28-29 of the specification. Support for the amendment to claim 7 can be found in the specification on page 78, line 19-page 79, line 14.

**Written Description Rejection Under 35 U.S.C. § 112**

Claim 7 stands rejected under 35 U.S.C. § 112 first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the specification only supports a single species of the claimed antibody and further alleges that there is no written support for the limitation "at least about 80%."

Applicants have deleted the phrase "at least about 80%" from claim 7, thus obviating the rejection.

**The Rejections Under 35 U.S.C. § 102(e)**

Claims 2-7, 10-13 and 24 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Korman et al. (US 2002/0086014 A1) ("Korman"). Claims 2, 10, 11, 13 and 24 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Lowman et al. (U.S. Patent No. 5,994,511) ("Lowman").

**A. The Anticipation Standard**

The standard required for finding anticipation under 35 U.S.C. § 102(e) is stated in MPEP § 2131 (emphasis added). "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim'. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)." Neither Korman or Lowman meet this standard.

**The Korman Reference**

The Office alleges that Korman teaches anti-CTLA4 antibody conjugates and that anti-CTLA4 antibodies can block or antagonize signals transduced by human CTLA4. The Office further alleges that given such inhibitory properties of anti-CTLA4 antibodies, the claimed specificity and functional properties recited in claims 5-7 are inherent properties of anti-CTLA4 antibodies. Applicants respectfully traverse the rejection.

Korman does not anticipate the claimed invention because its priority document (provisional application 60/150,452) does not disclose each and every element as set forth in the amended claim, either expressly or inherently. Applicants note that the filing date of the cited Korman application (US 2002/0086014 A1) is September 7, 2001. Korman claims priority (as a continuation-in-part) to application serial number 09/644,668, filed August 24, 2000 and to provisional application number 60/150,452, filed August 24, 1999. The instant application has a priority date of January 27, 2000. Thus, to be anticipatory, Korman must disclose each and every element of the claimed invention in the provisional application filed on August 24, 1999. Korman does not meet this requirement.

Amended claim 2 recites that the soluble monoclonal antibody-toxic moiety conjugate binds to and inhibits proliferation of a T cell. Korman does not disclose a soluble monoclonal antibody toxic moiety conjugate wherein the antibody-toxic moiety conjugate binds to and inhibits proliferation of a T cell. According to Korman anti-CTLA4 antibodies only inhibit an immune response if they are crosslinked to a microsphere and thus are insoluble, multivalent, or polyclonal. The Korman antibodies recognize at least two different CTLA4 epitopes (see Korman provisional application

60/150,452 page 48, lines 4-35). The amended claim states the antibodies are soluble and monoclonal; thus, they cannot be conjugated to a microsphere or polyclonal.

Korman describes multivalent antibodies as antibodies crosslinked to each other to form multimers or alternatively genetically engineered hybrids comprising the constant regions of IgM or IgA (see Korman provisional application 60/150,452 page 48, lines 4-35). In contrast, the instant specification describes an antibody as follows:

> The term "antibody," as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds (page 10, lines 13-15).

The specification also provides for antibody fragments that specifically bind CTLA4:

> The term "antibody" as used herein also includes an "antigen binding portion" of an antibody (or simply "antibody portion"). The term "antibody binding portion," as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hCTLA4). It has been shown that the antigen binding function of an antibody can be performed by fragments of a full length antibody (page 11, lines 1-6).

Thus, when the claims are read in light of the specification, they do not read on the multivalent, polyclonal or insoluble antibodies which are the only CTLA4 specific antibodies Korman suggests can inhibit an immune response.

The Office also alleges that claims 5-7 are inherently anticipated by Korman. Claim 5 recites that the antibody toxic moiety conjugate binds to a region of the CTLA4 molecule that blocks the binding of CTLA4 to CD80 or CD86. Claim 6 recites that the antibody toxic moiety conjugate binds to a region of the CTLA4 in spatial proximity to the site of CTLA4 binding to a costimulatory molecule. Claim 7 merely describes the

effect of one mutation in a CTLA4 on binding affinity of the antibody toxic moiety conjugate.

Applicants submit that these claims are not inherently anticipated by Korman because not all CTLA4 antibodies disclosed by Korman can inhibit proliferation of a T cell. Moreover, not all antibodies block CD80 or CD86 binding, or bind in spatial proximity to CD80 or CD86. "Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient," *In re King*, 231 U.S.P.Q. 136, 138 (Fed. Cir. 1986). Korman does not meet this standard. Korman discloses that anti-CTLA4 can be immunostimulatory (e.g. when they are soluble and block CTLA4 binding to a B7 molecule) and immuno-inhibitory when they are crosslinked, multivalent or polyclonal (see provisional application 60/150,452 page 48, lines 4-10). Accordingly, claims 5-7 are not inherently anticipated by Korman. Applicants submit that Korman does not anticipate the claimed invention.

**The Lowman Reference**

The Office alleges that Lowman discloses antibodies against a variety of antigens including CTLA4. The Office further alleges that Lowman discloses the antibodies can be conjugated, monoclonal and humanized. The Office also alleges that the claimed functional limitations would be inherent properties of the antibodies disclosed in Lowman. Applicants respectfully traverse this rejection.

Lowman does not disclose a soluble monoclonal antibody toxic moiety conjugate which specifically binds to CTLA4 and inhibits T cell proliferation. Lowman does not

disclose any immune suppression mediated by CTLA4 specific antibodies. Indeed, Lowman does not disclose any function associated with CTLA4 specific antibodies. Lowman discusses the use of phage display to alter antibody affinity. CTLA4 is merely mentioned as one of many potential targets for these improved antibodies. Moreover, Lowman does not inherently anticipate the claimed invention, because not all CTLA4 antibodies inhibit proliferation of a T cell, *see, e.g.*, Korman (US 2002/0086014 A1)(cited by the Office in this office action). Korman discloses that CTLA4 antibodies can be immuno-stimulatory and immuno-inhibitory. Because some CTLA4 specific antibodies stimulate an immune response, the allegation that any CTLA4 specific antibody would possess the functional limitations of the claimed invention must fail. Accordingly, Lowman does not anticipate, either inherently or directly.

For the reasons stated above, Applicants respectfully submit that neither Lowman or Korman anticipate the invention and therefore, Applicants request withdrawal of the rejection under 35 U.S.C. § 102(e).

**The Rejections Under 35 U.S.C. § 103(a)**

Claims 2-11, 13 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Korman et al. and/or Lowman in view of Hamann et al. (U.S. Patent No. 5,773,001) (Hamann). Claims 2-11,13 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,821,332 (Godfrey) and U.S. Patent No. 6,207,156 (Kuchroo) in view of Hamann.

**The Claimed Invention Is Not Prima Facie Obvious**

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine what the reference teaches. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, not the Applicant's disclosure. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desirability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.,* 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141. The Patent and Trademark Office (PTO) bears the burden of initially establishing a prima facie case of obviousness. MPEP § 2142. The PTO has not met its burden in the instant case.

**Korman and/or Lowman in View of Hamann**

The Office alleges that Korman teaches anti-CTLA4 antibodies including antibodies conjugated to toxic moieties. The Office further alleges the antibodies can be monoclonal and humanized. The Office also alleges that Korman teaches anti-CTLA4 antibodies that block or antagonize signals transduced by human CTLA4, including interactions between CTLA4 and B7. The Office further alleges that Lowman teaches antibodies against a variety of antigens, including CTLA4. The Office admits

that Lowman does not teach CTLA4 interaction with B7. The Office also alleges that Hamann discloses conjugation of a specific toxin (calcicheamicin) to a non-CTLA4 specific antibody. Applicants respectfully traverse this rejection.

**The Cited References Do Not Teach or Suggest All of The Claim Limitations**

The claims, as amended herein, recite "A soluble monoclonal antibody toxic moiety conjugate . . . wherein the antibody-toxic moiety conjugate binds to and inhibits proliferation of a T cell." As discussed above, Korman does not teach all of the claim limitations because Korman does not disclose a soluble, monoclonal, non-multimeric CTLA4 specific antibody that inhibits T cell proliferation. None of the other cited references cure this defect. Lowman merely discloses the possibility of making antibodies that recognize many different antigens. CTLA4 is merely one of a laundry list of such antigens. Nothing in Lowman suggests the possibility of modulating an immune response with CTLA4 specific antibodies. Hamann does not disclose any CTLA4 specific antibodies at all, but instead discloses ACT4 specific antibodies conjugated to specific toxins. Missing from all of these references is a soluble monoclonal antibody, as described in claim 2, which inhibits proliferation of a T cell. Because combining the cited references, does not teach or suggest all of the claim limitations the claims are not obvious in light of Korman and/or Lowman in view of Hamann.

**No Reasonable Expectation of Success Exists In Combining the Cited References**

There would be no reasonable expectation of success in combining Korman and/or Lowman with Hamann because none of the references teach that "a soluble

monoclonal antibody" specifically recognizing CTLA4 can be successfully used to inhibit T cell proliferation. As stated above, only the Korman reference discusses the possibility of immune suppression using CTLA4 specific antibodies, and Korman requires either multivalent, polyclonal or insoluble crosslinked antibodies. Nothing in any of the other references cited would suggest that T cell proliferation could be inhibited using a soluble monoclonal CTLA4 specific antibody.

Moreover, Korman teaches away from the claimed invention by suggesting that soluble CTLA4 specific antibodies enhance, not inhibit, an immune response (see provisional application 60/150,452 page 48, lines 4-10). Additionally, Korman discloses that any CTLA4 antibody that blocks B7 binding will enhance an immune response (see provisional application 60/150,452 page 15, lines 11-32). Accordingly, a skilled artisan reading the cited references would have no reasonable expectation of success that "a soluble monoclonal antibody" specific to CTLA4 could be used to inhibit T cell proliferation. Applicants therefore submit that the claimed invention is not obvious in light of these references.

**Kuchroo Combined With Godffrey In View of Hamann**

The Office alleges Kuchroo teaches monoclonal antibodies to CTLA4, but admits that Kuchroo does not teach antibody toxic-moiety conjugates. The Office alleges that Godfrey teaches antibody-toxic moiety conjugates specific to ACT4, a polypeptide expressed only on activated T cells. The Office concludes the claimed invention is obvious in light of Godfrey combined with Kuchroo. The conclusion is erroneous.

**The Cited References Do Not Teach or Suggest All of The Claim Limitations**

None of cited references teach or suggest a soluble monoclonal antibody-toxic moiety conjugate wherein the antibody-toxic moiety conjugate binds to and inhibits T cell proliferation. None of the cited references teach inhibition of T cell proliferation using a CTLA4 specific antibody. Because the combination of the cited references fails to teach all of the claim limitations, the claimed invention is not obvious in light of Kuchroo combined with Godfrey in view of Hamann.

**No Reasonable Expectation of Success Exists In Combining the Cited References**

There would be no reasonable expectation of success in combining Kuchroo with Godfrey, because Godfrey discloses a CTLA4 specific antibody that is immunostimulatory. But nothing in any reference cited by the Office suggests conjugating a toxin to an immunostimulatory antibody would be successful. As admitted by the Office, the conjugated antibody to ACT4 disclosed by Godfrey was not immunostimulatory. As further admitted by the Office, the CTLA4 antibody disclosed by Kuchroo was. The Office admits that conjugation of a toxin to an antibody is supposed to target that cell for elimination. But nothing of record indicates that conjugating a toxin to a CTLA4 specific antibody would be successful, given that Kuchroo discloses that CTLA4 specific antibodies cause T cells to proliferate (i.e. are immunostimulatory). The Office suggests combining two compositions which have opposing outcomes (i.e. a toxin which eliminates cells combined with an antibody that causes the same cells to proliferate). At best, the combination might be merely obvious to try, but there was certainly no reasonable expectation of success that the combination would be

successful. Obvious to try, however, is not the standard under 35 U.S.C. § 103. *In re O'Farrell*, 7 U.S.P.Q. 1673, 1680 (Fed. Cir. 1988).

The Office now states that "the ordinary artisan would have appreciated that even though in certain instances antibodies to CTLA4 may be used to enhance an immune response, CTLA4 could also serve as a target for the elimination of T cells when the T cells were participating in an undesired immune response" (Office Action dated January 26, 2004, page 9). But the Office points to no reference of record to support this position. The Office is reminded that the reasonable expectation of success must be found in the cited references. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicants submit the Office has not met its burden in this regard and respectfully request the rejection be withdrawn.

Applicants previously argued that no reasonable expectation of success existed in making the claimed combination because CTLA4 and ACT4 belonged to distinct families and each was a member of a distinct signaling pathway. In response, the Office argued the instant claims are drawn to a product and the motivation of the ordinary artisan to produce the instantly claimed product would not have been inhibited by the fact that CTLA4 and ACT4 belong to different families or the uniqueness of ACT4. The Office further argued antibody linked toxins to a variety of receptor families were well known at the time of the invention and the identification of cell surface molecules expressed predominantly on activated T cells provided the artisan with the opportunity to selectively eliminate activated T cells. There is nothing of record to support any of these statements. The Office is respectfully reminded that the burden of establishing a prima facie case of obviousness rests with the Office. MPEP § 2142.

Applicants request that the Office cite a reference to support its position. Alternatively, if the Office is relying on the personal knowledge of the Examiner to support its position, Applicants request the submission of an affidavit pursuant 37 C.F.R. §1.104(d). Without such support Applicants submit the rejection must be withdrawn.

**No Motivation To Combine The Cited References Exists**

A skilled artisan would not be motivated to combine the cited references because Godfrey and Kuchroo teach contradictory outcomes. Targeting a cell with a toxic moiety attached to an ACT4 specific antibody is intended to eliminate the target cell. Targeting a cell with the CTLA4 antibody disclosed in Kuchroo is intended to make the target cell proliferate. The Office has not pointed to anything in either reference to establish why such a combination would be desirable. The references do not provide any motivation for a skilled artisan to combine them and the Office has not pointed to any knowledge generally available to a skilled artisan to suggest such a combination would be desirable. Accordingly, Applicants respectfully request withdrawal of the rejection.

**Hamann Combined With Godfrey And Kuchroo Does Not Render Claims 8 And 9 Prima Facie Obvious**

Additionally, claims 8-9 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Godfrey, combined with Kuchroo in view of U.S. Patent No. 5,773,001 (Hamann). Claim 8 recites the toxic moiety is a carbohydrate. Claim 9 recites the carbohydrate is calicheamicin. Hamann teaches antibodies conjugated with calicheamicin. Hamman does not teach targeting molecules expressed on activated T cells. Thus, Hamman does not teach targeting CTLA4. The Office relies on Hamann as allegedly teaching antibodies conjugated to carbohydrates generally, and calicheamicin

specifically. Hamann, however, does not compensate for the deficiencies in the Godfrey and Kuchroo. A skilled artisan reading Hamann, would still have no reasonable expectation of success in combining Godfrey with Kuchroo, as Hamann only provides information on conjugating antibodies with calicheamicin--it does not address targeting CTLA4 or explain why an immunostimulatory antibody could be successfully conjugated to a toxin intended to kill the target cell of the antibody. Thus, claims 8 and 9 are not prima facie obvious.

Accordingly, for the reasons stated above Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: May 28, 2004

By: E Stewart Mittler
E. Stewart Mittler
Reg. No. 50,316